BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 257/00 — A2

(11) International Publication Number: WO 99/31074

(43) International Publication Date: 24 June 1999 (24.06.99)

(21) International Application Number: PCT/US98/23917

(22) International Filing Date: 10 November 1998 (10.11.98)

(30) Priority Data:

60/069,773	16 December 1997 (16.12.97)	US
60/104,924	20 October 1998 (20.10.98)	US

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BELLIOTTI, Thomas, Richard [US/US]; 6125 Lodi Lane, Saline, MI 48176 (US). BRYANS, Justin, Stephen [GB/GB]; Dean Cottage, 3 W. Wickham Road, Balsham CB1 6DZ (GB). CAPIRIS, Thomas [US/US]; 14816 Greenbriar Court, Plymouth, MI 48170 (US). HORWELL, David, Christopher [GB/GB]; 8 West Hill, Foxton, Cambridge CB2 6SZ (GB). KNEEN, Clare, Octavia [GB/GB]; Slade Cottage, Petts LN, Little Walden, Essex CB10 1XH (GB). WUSTROW, David, Juergen [US/US]; 5101 John Holmes Road, Ann Arbor, MI 48103 (US).

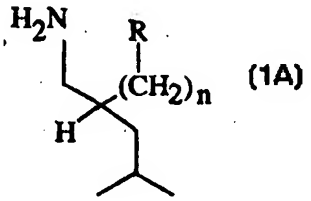
(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

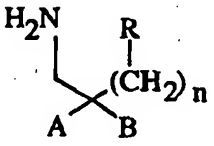
Published

Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL AMINES AS PHARMACEUTICAL AGENTS



(1A)



(1B)

(57) Abstract

Novel amines of formulas (1A) and (1B) are disclosed and are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, inflammatory diseases, and gastrointestinal disorders, especially IBS. Processes for the preparation and intermediates useful in the preparation are also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

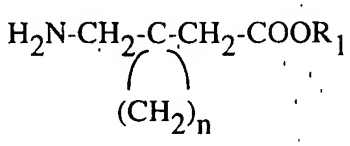
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NOVEL AMINES AS PHARMACEUTICAL AGENTS

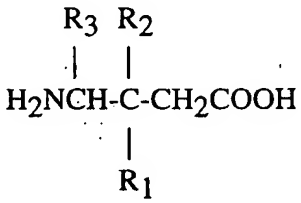
BACKGROUND OF THE INVENTION

Compounds of formula



wherein R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in United States Patent Number 4,024,175 and its divisional United States Patent Number 4,087,544. The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

Compounds of formula



wherein R_1 is a straight or branched alkyl group having from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R_2 is hydrogen or methyl; and R_3 is hydrogen, methyl, or carboxyl are known in United States Patent Number 5,563,175 and various divisionals. These patents are hereby incorporated by reference.

SUMMARY OF THE INVENTION

The compounds of the instant invention are novel amines and their pharmaceutically acceptable salts useful in a variety of disorders. The disorders include: epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, inflammation, and gastrointestinal disorders.

The compounds of the invention are those of formulas 1A and 1B below.

Preferred compounds are those of formulas 1A and 1B wherein R is a sulfonamide selected from $-NHSO_2R^{15}$ or $-SO_2NHR^{15}$ wherein R^{15} is straight or branched alkyl or trifluoromethyl.

Especially preferred are:

4-Methyl-2-(1H-tetrazol-5-ylmethyl)-pentylamine;

3-(2-Aminomethyl-4-methyl-pentyl)-4H-[1,2,4]oxadiazole-5-thione, HCl;

3-(2-Aminomethyl-4-methyl-pentyl)-4H-[1,2,4]oxadiazole-5-one, HCl;

(2-Aminomethyl-4-methyl-pentyl)-phosphonic acid;

3-(3-Amino-2-cyclopentyl-propyl)-4H-[1,2,4]oxadiazol-5-one;

3-(3-Amino-2-cyclopentyl-propyl)-4H-[1,2,4]thiadiazol-5-one;

2-Cyclopentyl-3-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-yl)-propylamine;

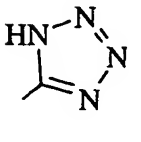
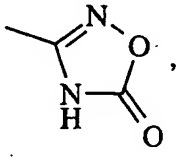
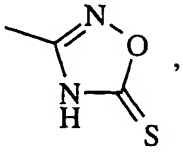
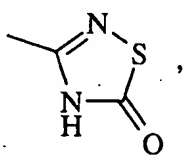
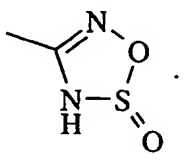
3-(3-Amino-2-cyclobutyl-propyl)-4H-[1,2,4]oxadiazol-5-one;

3-(3-Amino-2-cyclobutyl-propyl)-4H-[1,2,4]thiadiazol-5-one; and

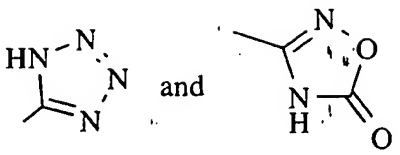
2-Cyclobutyl-3-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-yl)-propylamine.

Other preferred compounds are those of formulas 1A and 1B wherein R is a phosphonic acid, $-PO_3H_2$.

Other preferred compounds are those of Formulas 1A and 1B wherein

 ,  ,  ,  , and  .

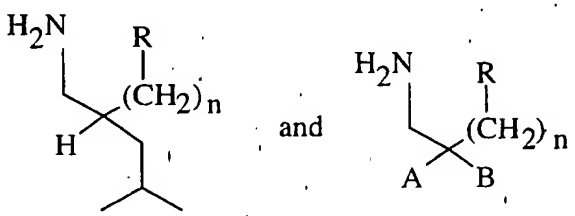
Especially preferred are:



DETAILED DESCRIPTION OF THE INVENTION

The amines of the instant invention are compounds of formula 1A and 1B and the pharmaceutically acceptable salts thereof.

The compounds of the invention are those of formula



1A 1B

or a pharmaceutically acceptable salt thereof wherein;

n is an integer of from 0 to 2;

R is sulfonamide,

amide,

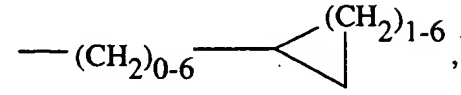
phosphonic acid,

heterocycle,

sulfonic acid, or

hydroxamic acid;

A is hydrogen or methyl; and

B is  ,

straight or branched alkyl of from 1 to 11 carbons, or

$-(CH_2)_{1-4}-Y-(CH_2)_{0-4}$-phenyl wherein Y is -O-, -S-, $-NR'_3$ wherein R'_3 is alkyl of from 1 to 6 carbons, cycloalkyl of from 3 to 8 carbons, benzyl or phenyl wherein benzyl or phenyl can be unsubstituted or substituted with from 1 to 3 substituents each independently selected from alkyl, alkoxy, halogen, hydroxy, carboxy, carboalkoxy, trifluoromethyl, and nitro.

Since amino acids are amphoteric, pharmacologically compatible salts can be salts of appropriate inorganic or organic acids, for example, hydrochloric, sulphuric, phosphoric, acetic, oxalic, lactic, citric, malic, salicylic, malonic, maleic, succinic, methanesulfonic acid, and ascorbic. Starting from corresponding hydroxides or carbonates, salts with alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium, or calcium are formed. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. The carboxyl group of the amino acids can be esterified by known means.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

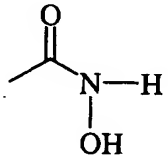
The terms used to define the invention are as described below.

Sulfonamides are those of formula $-NHSO_2R^{15}$ or $-SO_2NHR^{15}$ wherein R^{15} is a straight or branched alkyl group of from 1 to 6 carbons or a trifluoromethyl.

Amides are compounds of formula $-NHCOR^{12}$ wherein R^{12} is straight or branched alkyl of from 1 to 6 carbons, benzyl, and phenyl.

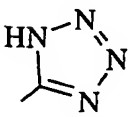
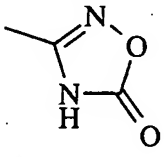
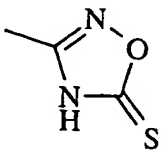
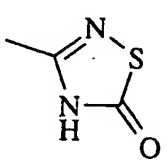
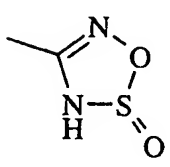
Phosphonic acids are $-PO_3H_2$.

Sulfonic acids are $-SO_3H$.

Hydroxamic acid is  .

Heterocycles are groups of from 1 to 2 rings, with from 1 to 6 heteroatoms selected from oxygen, nitrogen, and sulfur.

Preferred heterocycles are

 ,  ,  ,  , and  .

The term alkyl is a straight or branched group of from 1 to 11 carbon atoms including but not limited to methyl, ethyl, propyl, n-propyl, isopropyl, butyl, 2-butyl, tert-butyl, pentyl, hexyl, and n-hexyl, heptyl, octyl, nonyl, decyl, and undecyl except as where otherwise stated.

The cycloalkyl groups are from 3 to 8 carbons and are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl unless otherwise stated.

The benzyl and phenyl groups may be unsubstituted or substituted by from 1 to 3 substituents selected from hydroxy, carboxy, carboalkoxy, halogen, CF_3, nitro, alkyl, and alkoxy. Preferred are halogens.

Alkoxy is as defined above for alkyl.

Halogen is fluorine, chlorine, and bromine and preferred are fluorine and chlorine.

Carboalkoxy is -COOalkyl wherein alkyl is as described above. Preferred are carbomethoxy and carboethoxy.

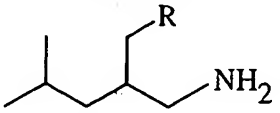
Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

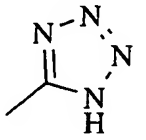
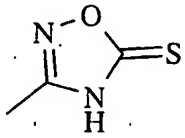
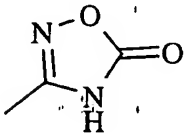
Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

The radioligand binding assay using [^{3}H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue was used ("The Novel Anti-convulsant Drug, Gabapentin, Binds to the $\alpha_2\delta$ Subunit of a Calcium Channel", Gee N.S., et al., J. Biol Chem, 1996;271(10):5768-5776).

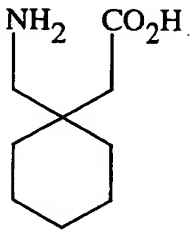
The compounds of the invention show good binding affinity to the $\alpha_2\delta$ subunit. Gabapentin (Neurontin®) is about 0.10 to 0.12 μM in this assay. Since the compounds of the instant invention also bind to the subunit, they are expected to exhibit pharmacologic properties comparable to gabapentin. For example, as agents for convulsions, anxiety, and pain.

TABLE 1

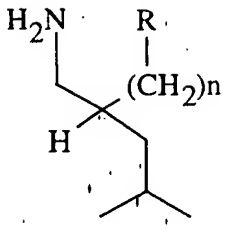


R	α2δ Assay IC_{50} (μM)	Pain Model % MPE		Vogel Conflict % of CI-1008	DBA2 % Protection	
		1 Hr	2 Hr		1 Hr	2 Hr
	2.47	0	0	0.0	0	0
	>10				0	0
	1.52					
PO_3H_2	>10				0	0

The compounds of the invention are related to Neurontin®, a marketed drug effective in the treatment of epilepsy. Neurontin® is 1-(aminomethyl)-cyclohexaneacetic acid of structural formula



Preferred novel gabapentin and isobutyl-GABA analogs, their derivatives, and pharmaceutically acceptable salts are useful in the treatment of a variety of disorders including epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, and neuropathological disorders. The compounds are of the general formula:



a pharmaceutically acceptable salt thereof or a prodrug thereof, where n = 0,1,2, m = 0,1,2,3, and R can be sulfonamides of the general formula $-NHSO_2R^1$ or $-SO_2NHR^1$ where R^1 is H or C_1-C_4 straight or branched chain alkyl or trifluoromethyl. R may also be an amide of the general formula $-NHCOR^1$. Or R may also be a phosphonic acid $-PO_3H_2$ (Lipinski C.A., Ann. Rep. Med. Chem., 21:283 (1986)).

The compounds of the invention are also expected to be useful in the treatment of epilepsy.

The present invention also relates to therapeutic use of the compounds of the mimetic as agents for neurodegenerative disorders.

Such neurodegenerative disorders are, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and epilepsy.

The present invention also covers treating neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia.

Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular incident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia such as in a patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like.

Pain refers to acute as well as chronic pain.

Acute pain is usually short-lived and is associated with hyperactivity of the sympathetic nervous system. Examples are postoperative pain and allodynia.

Chronic pain is usually defined as pain persisting from 3 to 6 months and includes somatogenic pains and psychogenic pains. Other pain is nociceptive.

Still other pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain diabetics suffer from.

Psychogenic pain is that which occurs without an organic origin such as low back pain, atypical facial pain, and chronic headache.

Other types of pain are: inflammatory pain, osteoarthritic pain, trigeminal neuralgia, cancer pain, diabetic neuropathy, restless leg syndrome, acute herpetic and postherpetic neuralgia, causalgia, brachial plexus avulsion, occipital neuralgia, gout, phantom limb, burn, and other forms of neuralgia, neuropathic and idiopathic pain syndrome.

Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, and hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia.

The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

The compounds of the invention are also expected to be useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a strong tendency for familial occurrence of some forms of depression suggesting a mechanistic cause for at least some forms of depression. The diagnosis of depression is made primarily by quantification of alterations in patients' mood. These evaluations of mood are generally performed by a physician or quantified by a neuropsychologist using validated rating scales, such as the Hamilton

Depression Rating Scale or the Brief Psychiatric Rating Scale. Numerous other scales have been developed to quantify and measure the degree of mood alterations in patients with depression, such as insomnia, difficulty with concentration, lack of energy, feelings of worthlessness, and guilt. The standards for diagnosis of depression as well as all psychiatric diagnoses are collected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) referred to as the DSM-IV-R manual published by the American Psychiatric Association, 1994.

GABA is an inhibitory neurotransmitter with the central nervous system. Within the general context of inhibition, it seems likely that GABA-mimetics might decrease or inhibit cerebral function and might therefore slow function and decrease mood leading to depression.

The compounds of the instant invention may produce an anticonvulsant effect through the increase of newly created GABA at the synaptic junction. If gabapentin does indeed increase GABA levels or the effectiveness of GABA at the synaptic junction, then it could be classified as a GABA-mimetic and might decrease or inhibit cerebral function and might, therefore, slow function and decrease mood leading to depression.

The compounds of the invention will be useful in the treatment of gastrointestinal disorders, especially irritable bowel syndrome.

The fact that a GABA agonist or GABA-mimetic might work just the opposite way by increasing mood and thus, be an antidepressant, is a new concept, different from the prevailing opinion of GABA activity heretofore.

The compounds of the instant invention are also expected to be useful in the treatment of anxiety and of panic as demonstrated by means of standard pharmacological procedures.

MATERIAL AND METHODS

Carrageenin-Induced Hyperalgesia

Nociceptive pressure thresholds were measured in the rat paw pressure test using an analgesymeter (Randall-Sellitto Method: Randall L.O., Sellitto J.J.,

A method for measurement of analgesic activity on inflamed tissue. Arch. Int. Pharmacodyn., 4:409-419 (1957)). Male Sprague-Dawley rats (70-90 g) were trained on this apparatus before the test day. Pressure was gradually applied to the hind paw of each rat and nociceptive thresholds were determined as the pressure (g) required to elicit paw withdrawal. A cutoff point of 250 g was used to prevent any tissue damage to the paw. On the test day, two to three baseline measurements were taken before animals were administered 100 µL of 2% carrageenin by intraplantar injection into the right hind paw. Nociceptive thresholds were taken again 3 hours after carrageenin to establish that animals were exhibiting hyperalgesia. Animals were dosed with either gabapentin (3-300 mg/kg, s.c.), morphine (3 mg/kg, s.c.), or saline at 3.5 hours after carrageenin and nociceptive thresholds were examined at 4, 4.5, and 5 hours post carrageenin.

Semicarbazide-Induced Tonic Seizures

Tonic seizures in mice are induced by subcutaneous administration of semicarbazide (750 mg/kg). The latency to the tonic extension of forepaws is noted. Any mice not convulsing within 2.0 hours after semicarbazide are considered protected and given a maximum latency score of 120 minutes.

Animals

Male Hooded Lister rats (200-250 g) are obtained from Interfauna (Huntingdon, UK) and male TO mice (20-25 g) are obtained from Bantin and Kingman (Hull, UK). Both rodent species are housed in groups of six. Ten Common Marmosets (Callithrix Jacchus) weighing between 280 and 360 g, bred at Manchester University Medical School (Manchester, UK) are housed in pairs. All animals are housed under a 12-hour light/dark cycle (lights on at 07.00 hour) and with food and water ad libitum.

Drug Administration

Drugs are administered either intraperitoneally (IP) or subcutaneously (SC) 40 minutes before the test in a volume of 1 mL/kg for rats and marmosets and 10 mL/kg for mice.

Mouse Light/Dark Box

The apparatus is an open-topped box, 45 cm long, 27 cm wide, and 27 cm high, divided into a small (2/5) and a large (3/5) area by a partition that extended 20 cm above the walls (Costall B., et al., Exploration of mice in a black and white box: validation as a model of anxiety. Pharmacol. Biochem. Behav., 32:777-785 (1989)).

There is a 7.5 × 7.5 cm opening in the center of the partition at floor level. The small compartment is painted black and the large compartment white. The white compartment is illuminated by a 60-W tungsten bulb. The laboratory is illuminated by red light. Each mouse is tested by placing it in the center of the white area and allowing it to explore the novel environment for 5 minutes. The time spent in the illuminated side is measured (Kilfoil T., et al., Effects of anxiolytic and anxiogenic drugs on exploratory activity in a simple model of anxiety in mice. Neuropharmacol., 28:901-905 (1989)).

Rat Elevated X-Maze

A standard elevated X-maze (Handley S.L., et al., Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behavior. Naunyn-Schiedeberg's Arch. Pharmacol., 327:1-5 (1984)), was automated as previously described (Field, et al., Automation of the rat elevated X-maze test of anxiety. Br. J. Pharmacol., 102(Suppl):304P (1991)). The animals are placed on the center of the X-maze facing one of the open arms. For determining anxiolytic effects the entries and time spent on the end half sections of the open arms is measured during the 5-minute test period (Costall, et al., Use of the elevated plus maze to assess anxiolytic potential in the rat. Br. J. Pharmacol., 96(Suppl):312P (1989)).

Marmoset Human Threat Test

The total number of body postures exhibited by the animal towards the threat stimulus (a human standing approximately 0.5 m away from the marmoset cage and staring into the eyes of the marmoset) is recorded during the 2-minute test period. The body postures scored are slit stares, tail postures, scent marking of the cage/perches, piloerection, retreats, and arching of the back. Each animal is

exposed to the threat stimulus twice on the test day before and after drug treatment. The difference between the two scores is analyzed using one-way analysis of variance followed by Dunnett's t-test. All drug treatments are carried out SC at least 2 hours after the first (control) threat. The pretreatment time for each compound is 40 minutes.

Rat Conflict Test

Rats are trained to press levers for food reward in operant chambers. The schedule consists of alternations of four 4-minute unpunished periods on variable interval of 30 seconds signaled by chamber lights on and three 3-minute punished periods on fixed ratio 5 (by footshock concomitant to food delivery) signaled by chamber lights off. The degree of footshock is adjusted for each rat to obtain approximately 80% to 90% suppression of responding in comparison with unpunished responding. Rats receive saline vehicle on training days.

The compounds of the instant invention are also expected to be useful in the treatment of pain and phobic disorders (Am. J. Pain Manag., 5:7-9 (1995)).

The compounds of the instant invention are also expected to be useful in treating the symptoms of manic, acute or chronic, single upside, or recurring depression. They are also expected to be useful in treating and/or preventing bipolar disorder (United States Patent Number 5,510,381).

TNBS-Induced Chronic Visceral Allodynia In Rats

Injections of trinitrobenzene sulfonic (TNBS) into the colon have been found to induce chronic colitis. In human, digestive disorders are often associated with visceral pain. In these pathologies, the visceral pain threshold is decreased indicating a visceral hypersensitivity. Consequently, this study was designed to evaluate the effect of injection of TNBS into the colon on visceral pain threshold in a experimental model of colonic distension.

Animals and Surgery

Male Sprague-Dawley rats (Janvier, Le Genest-St-Ilse, France) weighing 340-400 g are used. The animals are housed 3 per cage in a regulated environment (20 ± 1°C, 50 ± 5% humidity, with light 8:00 am to 8:00 pm). Under anesthesia

(ketamine 80 mg/kg ip; acepromazin 12 mg/kg ip), the injection of TNBS (50 mg/kg) or saline (1.5 mL/kg) is performed into the proximal colon (1 cm from the cecum). After the surgery, animals are individually housed in polypropylene cages and kept in a regulated environment (20 ± 1°C, 50.± 5% humidity, with light 8:00 am to 8:00 pm) during 7 days.

Experimental Procedure

At Day 7 after TNBS administration, a balloon (5-6 cm length) is inserted by anus and kept in position (tip of balloon 5 cm from the anus) by taping the catheter to the base of the tail. The balloon is progressively inflated by step of 5 mm Hg, from 0 to 75 mm Hg, each step of inflation lasting 30 seconds. Each cycle of colonic distension is controlled by a standard barostat (ABS, St-Dié, France). The threshold corresponds to the pressure which produced the first abdominal contraction and the cycle of distension is then discontinued. The colonic threshold (pressure expressed in mm Hg) is determined after performance of four cycles of distension on the same animal.

Determination of the Activity of the Compound

Data is analyzed by comparing test compound-treated group with TNBS-treated group and control group. Mean and sem are calculated for each group. The antiallodynic activity of the compound is calculated as follows:

Activity (%) = (group C – group T) / (group A – group T)

Group C: mean of the colonic threshold in the control group

Group T: mean of the colonic threshold in the TNBS-treated group

Group A: mean of the colonic threshold in the test compound-treated group

Statistical Analysis

Statistical significance between each group was determined by using a one-way ANOVA followed by Student's unpaired t-test. Differences were considered statistically significant at $p < 0.05$.

Compounds

TNBS is dissolved in EtOH 30% and injected under a volume of 0.5 mL/rat. TNBS is purchased from Fluka.

Oral administration of the test compound or its vehicle is performed 1 hour before the colonic distension cycle.

Sub-cutaneous administration of the test compound or its vehicle is performed 30 minutes before the colonic distension cycle.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the

formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

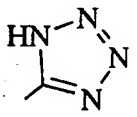
The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit

dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

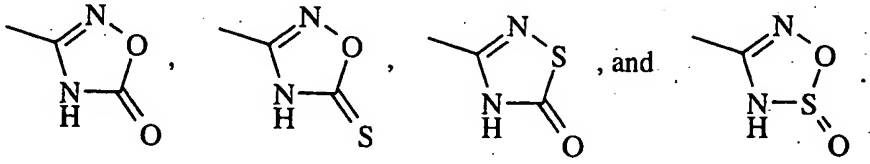
The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active component. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

R may also be a heterocycle such as tetrazole



or other heterocycles which have been used as replacements for CO_2H, such as

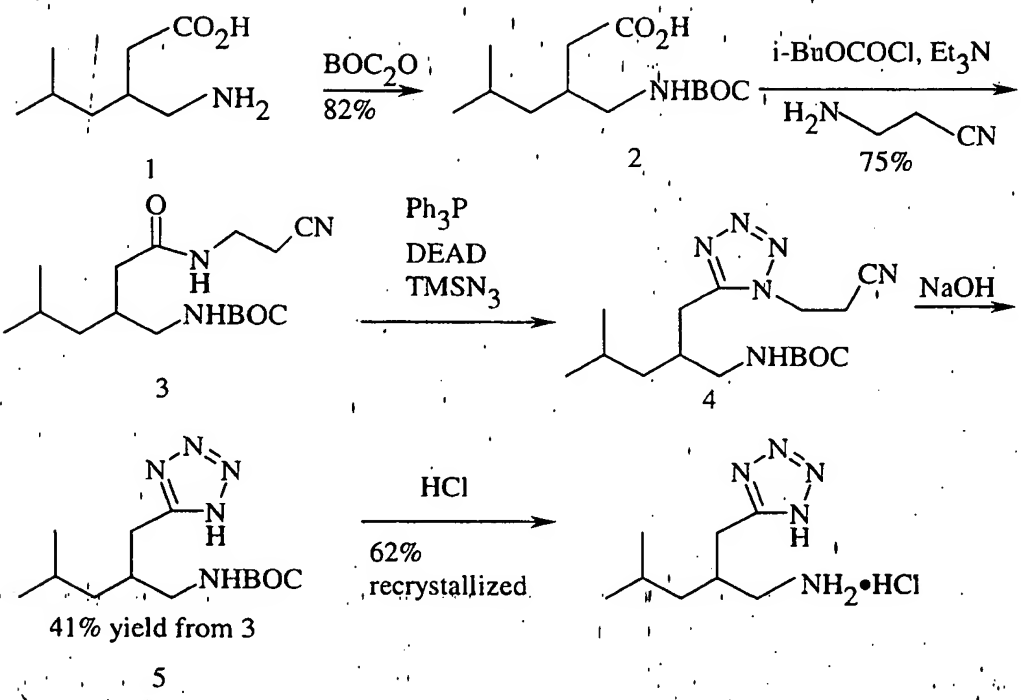


(Kohara Y., Kubo K., Imamiya E., Wada T., Inada Y., and Naka T., J. Med. Chem., 39:5228 (1996)).

Sulfonic and hydroxamic acids are also preferred.

Tetrazoles of Formula 1A can be synthesized by the route outlined in Scheme 1.

Scheme 1



1 2 3 4 5

The following examples are illustrative of the instant invention; they are not intended to limit the scope.

EXAMPLE 1

4-Methyl-2-(1H-tetrazol-5-ylmethyl)-pentylamine

Compound 3 in Scheme 1 {2-[(2-Cyano-ethylcarbamoyl)-methyl]-4-methyl-pentyl}-carbamic acid tert-butyl ester

A solution of compound 2 (8.0 g, 0.03 mol) (prepared in the usual manner from $(BOC)_2$ and pregabalin) was taken up in 250 mL dry THF and cooled in an ice water bath. Triethyl amine (4.62 mL, 0.033 mol) was added followed by the addition of isobutyle chloroformate (4 mL, 0.031 mol). The reaction was stirred at 0°C for about 15 minutes during which time a precipitate formed. In a separate flask was placed 3-aminoproprionitrile fumarate (3.95 g, 0.03 mol) in 35 mL of 1 M NaOH and 300 mL of THF. This mixture was cooled to 0°C and treated with the mixed anhydride formed above in four portions. Before each portion was

added, 35 mL of 1 M NaOH was added to the mixture. The reaction was stirred for 24 hours and was then concentrated to remove THF. The resulting aqueous was extracted with three times ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate. The solvents were removed under reduced pressure to give 6.6 g green oil. MS(APCI) m/z 312 (M + 1).

Compound 4 in Scheme 1 [4-Methyl-2-(1-(2-cyano-ethyl)-tetrazol-5-ylmethyl)-pentyl]-carbamic acid tert-butyl ester and compound 5 [4-Methyl-2-(1H-tetrazol-5-ylmethyl)-pentyl]-carbamic acid tert-butyl ester.

The cyanoamide (6.5 g, 0.0209 mol) and triphenylphosphine (11.06 g, 0.042 mol) were dissolved in 300 mL of dry THF. The solution was treated with DEAD (6.7 mL, 0.0425 mol) and $TMSN_3$ (5.75 mL, 0.043 mol). The reaction was stirred for 24 hours, and the reaction mixture was cooled to 0°C and treated with 900 mL of an aqueous solution containing 46.9 g of $(NH_4)_2Ce(IV)NO_3$. The reaction mixture was concentrated to remove THF and extracted with three portions of CH_2Cl_2. The combined organic layers were dried with brine and Na_2SO_4 and the solvents were removed under reduced pressure to give a clear oil which was passed through a plug of silicagel to give the product admixed with triphenylphospine oxide. This crude mixture was dissolved in 200 mL THF and 50 mL of 2N NaOH. The mixture was heated to reflux for 2 hours then stirred at room temperature overnight. The THF was removed under reduced pressure and the resulting residue diluted with water. After extraction with ether, the aqueous phase was acidified to pH 7 and extracted with 21 mL of 4N HCl. The aqueous phase was then saturated with solid KH_2PO_4. The aqueous mixture was extracted with CH_2Cl_2. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of the organic solvents under reduced pressure resulted in isolation of 3.4 g of an amber oil.

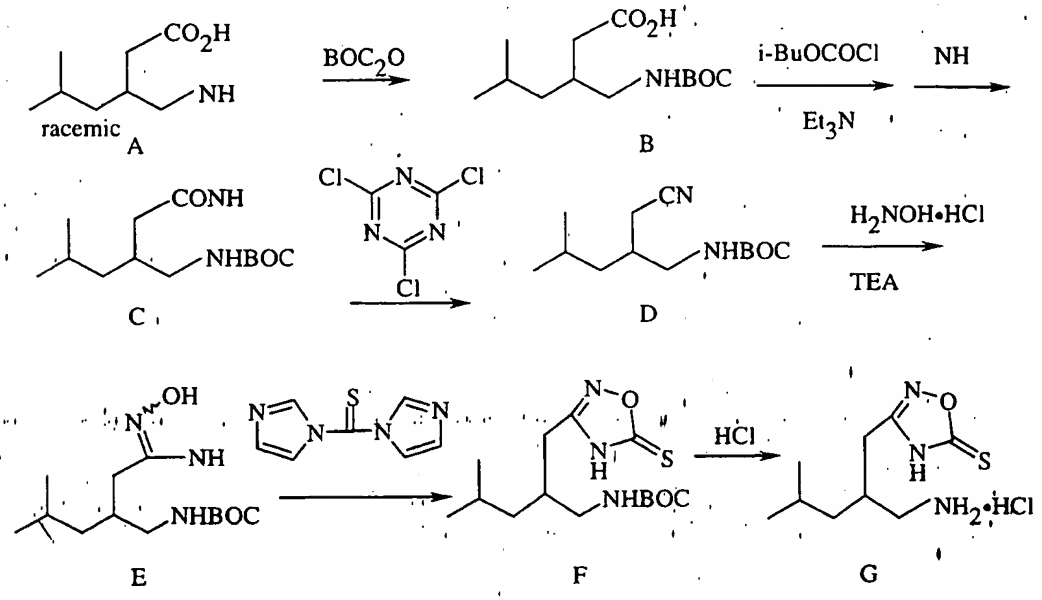
4-Methyl-2-(1H-tetrazol-5-ylmethyl)-pentylamine

The material from the previous step (0.9 g, 3.18 mmol) was taken up in 20 mL of 4 M HCl in dioxane. The reaction was allowed to stand for 1 hour. A

solid formed, 10 mL of ether was added, and the reaction was filtered to give 780 mg white solid. MS(APCI) m/z 184 (M + 1).

EXAMPLE 2

IsobutylGABA oxadiazolonethione (G) is also named 3-(2-Aminomethyl-4-methyl-pentyl)-4H-[1,2,4]oxadiazole-5-thione; HCl



BOC-IsobutylGABA (B)

A solution of di-tert-butyl dicarbonate (13.1 g, 0.06 mol) in THF (200 mL) was added, over a 10-minute period, to a solution of isobutylGABA (9.95 g, 0.056 mol) in 1N NaOH (125 mL) and THF (50 mL) cooled in an ice-water bath. The reaction mixture was stirred at room temperature 3 hours, concentrated to remove THF, saturated with saturated KH_2PO_4 and extracted 3× EtOAc. The extracts were washed 2× brine, dried over $MgSO_4$, and evaporated to yield 13.8 g (95%) of a white solid, mp 84-88°C. MS (APCI) m/z 260 (M+1).

BOC-IsobutylGABA amide (C)

A solution of BOC-IsobutylGABA (6.78 g, 0.026 mol) and triethylamine (3.0 g, 0.030 mol) was cooled to 0°C and isobutyl chloroformate (3.9 g, 0.029 mol) was slowly added. After stirring 20 minutes at 0°C, ammonia gas was

bubbled into the reaction mixture for 30 minutes, and then the mixture was stirred at room temperature 18 hours. The mixture was concentrated to remove THF, suspended in water, and extracted 3× EtOAc. The extracts were washed 1× 10% Na_2CO_3, 2× brine, and dried over Na_2SO_4. Evaporation yielded 4.9 g (73%) of an oil which was used without further purification. MS (APCI) m/z 259 (M+1).

BOC-IsobutylGABA nitrile (D)

A solution of BOC-IsobutylGABA amide (4.6 g, 0.0178 mol) in DMF (15 mL) was added, all at once, to cyanuric chloride (1.66 g, 0.009 mol) and stirred 30 minutes at room temperature. The reaction mixture was poured into a cold solution of $NaHCO_3$ (4.2 g, 0.05 mol) in water (150 mL). Solid K_2CO_3 was added to bring the pH to 9 and the mixture was extracted 2× CH_2Cl_2, washed 1× brine, and dried over Na_2SO_4. Evaporation yielded an oil, which was filtered through silica gel, eluting with CH_2Cl_2-EtOAc which yielded 3.8 g oil (89%), which was used without further purification. MS (APCI) m/z 240 (M), 239 (M-1); IR (Film) 2215 cm^{-1}.

BOC-IsobutylGABA amidoxime (E)

A solution of hydroxylamine was prepared by adding triethylamine (7.62 g, 0.075 mol) to a suspension of hydroxylamine hydrochloride (5.21 g, 0.075 mol) in DMSO (25 mL). After 15 minutes, the triethylamine hydrochloride was filtered off, and BOC-IsobutylGABA nitrile (3.61 g, 0.015 mol) was added to the filtrate. The mixture was heated at 75°C for 17 hours. The mixture was diluted with water and extracted 3× EtOAc. The extracts were washed 2× brine, dried over Na_2SO_4, and evaporated to give an oil which was filtered through a short silica gel column, eluting with CH_2Cl_2-EtOAc to give 3.2 g (78%) oil. ^1H NMR ($CDCl_3$) δ 0.84 (d, 6H, J = 6.35 Hz), 1.11 (m, 2H), 1.40 (s, 9H), 1.63 (m, 1H), 3.05 (m, 1H), 3.15 (m, 1H), 4.85 (m, 1H), 5.43 (m 1H); MS (APCI) 274 (M+1).

BOC-IsobutylGABA oxadiazolonethione (F)

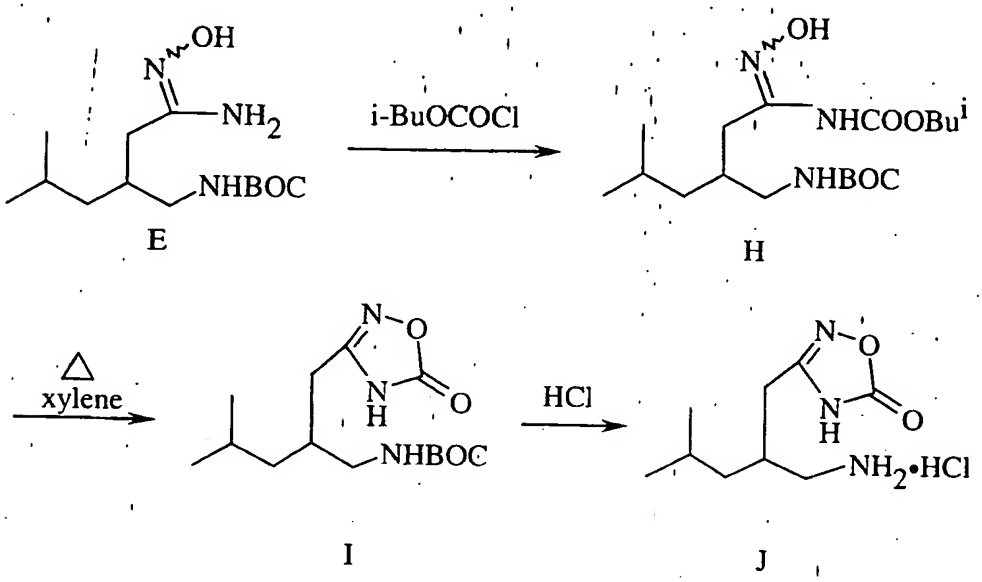
A solution containing BOC-Isobutyl GABA amidoxime (0.5 g, 0.00183 mol), DBU (1.12 g, 0.00736 mol) and 90% 1,1'-thiocarbonyldiimidazole (0.398 g, 0.002 mol) in MeCN (12 mL) was stirred at room temperature 16 hours. The reaction mixture was evaporated to dryness, taken up in EtOAc, and washed with $KHSO_4$ solution. The EtOAc layer was extracted with 1N NaOH (100 mL). The alkaline extract was washed with Et_2O and acidified with saturated KH_2PO_4 and extracted 3× EtOAc. The extracts were washed 1× water, 1× brine and dried over $MgSO_4$. Evaporation yielded an oil, 0.25 g (43%). ^1H NMR ($CDCl_3$) δ 0.84 (d, 6H, J = 6.59 Hz), 1.1 (m, 2H), 1.41 (s, 9H), 1.65 (m, 1H), 1.85 (m, 1H), 2.60 (m, 2H), 3.1 (m, 2H), 4.94 (m, 1H), 12.8 (s, 1H). MS (APCI) 316 (M+1).

IsobutylGABA oxadiazolonethione (G) is also named 3-(2-Aminomethyl-4-methyl-pentyl)-4H-[1,2,4]oxadiazole-5-thione; HCl.

BOC-IsobutylGABA oxadiazolonethione (0.25 g, 0.79 mmol) was taken up in 4 M HCl in dioxane (10 mL) at room temperature for 1 hour. Evaporation followed by recrystallization of the residue from MeCN yielded cream-colored crystals, 0.108 g, mp 183-185°C. ^1H NMR (DMSO-d_6) δ 0.84 (d, 6H, J = 6.59 Hz), 1.1 (m, 2H), 1.41 (s, 9H), 1.65 (m, 1H), 0.80 (d, 6H, J = 6.59 Hz), 1.06 (m, 1H), 1.25 (m, 1H), 1.55 (m, 1H), 2.1 (m, 1H), 2.7 (m, 4H), 7.95 (s, 3H); MS (APCI) 216 (M+1). Anal. Calcd for $C_9H_{17}N_3OS \cdot HCl$: C, 42.93; H, 7.21; N, 16.69; Cl, 14.08. Found: C, 43.38; H, 7.24; N, 16.29; Cl, 14.17.

EXAMPLE 3

IsobutylGABA oxadiazolone (J) is also named 3-(2-Aminomethyl-4-methyl-pentyl)-4H-[1,2,4]oxadiazole-5-one; HCl



BOC-IsobutylGABA amidoxime carbamate (H)

Isobutyl chloroformate (0.253 g, 0.00185 mol) was added dropwise to a solution of BOC-IsobutylGABA amidoxime (0.5 g, 0.00183 mol) and pyridine (0.158 g, 0.002 mol) in DMF (10ml) at 0°C. After 30 minutes at that temperature, the reaction mixture was diluted with water and extracted 3× EtOAc. The extracts were washed 1× water, 1× brine and dried over $MgSO_4$. Evaporation yielded an oil, 0.7 g (100%) which was used without further purification. MS (APCI) m/z 374 (M+1).

BOC-IsobutylGABA oxadiazolone (I)

BOC-IsobutylGABA amidoxime carbamate (0.7 g, 0.00183 mol) was taken up in xylene (20 mL) and heated under reflux 2 hours. Evaporation yielded a dark glassy oil which was taken up in Et_2O and extracted with 1N NaOH. The alkaline phase was acidified with saturated KH_2PO_4 and extracted 3× EtOAc. The extracts were washed with brine, dried over $MgSO_4$ and evaporated to yield a

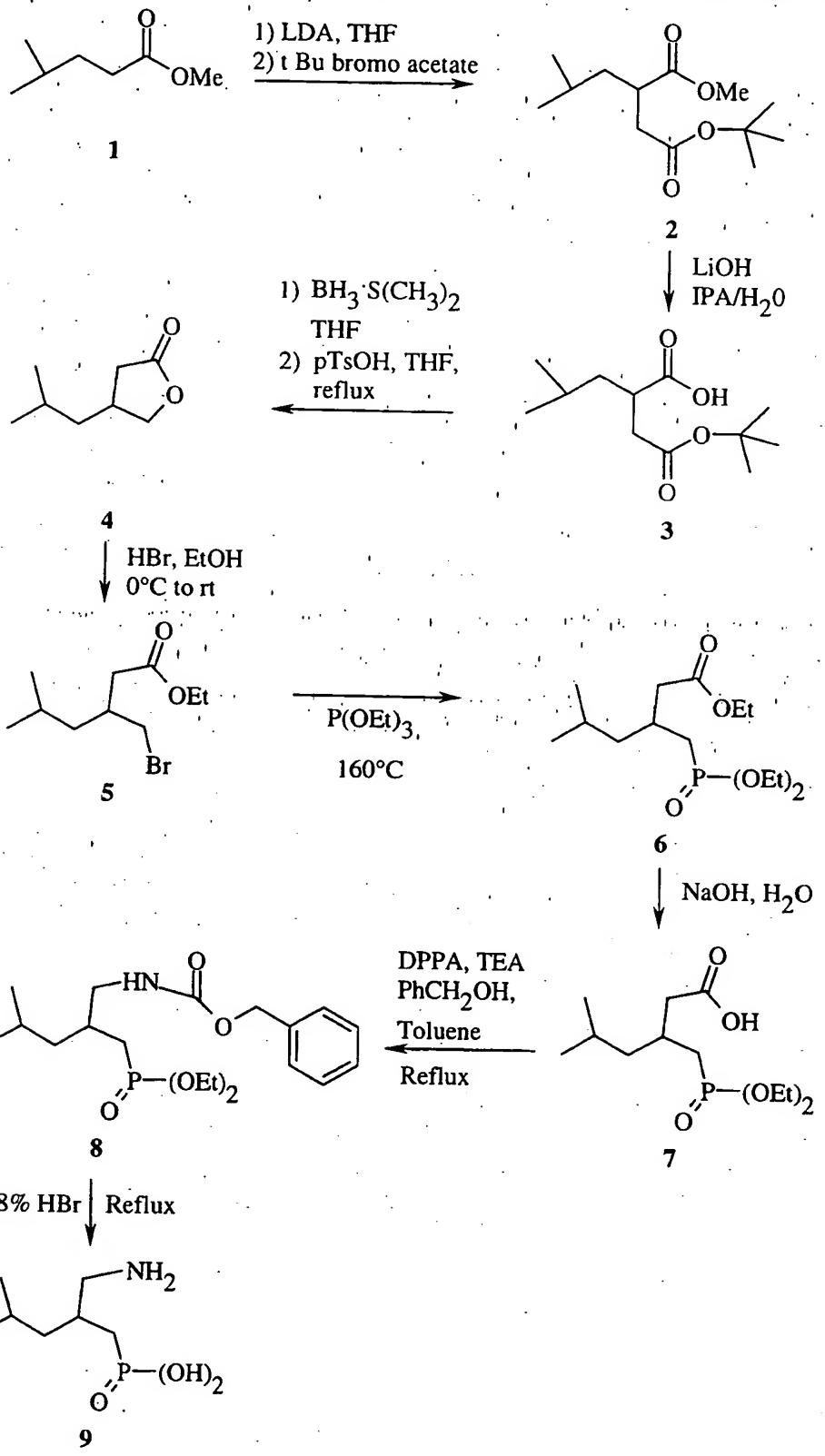
brown oil, 0.25 g (46%), which was used without further purification. MS (APCI) m/z 300 (M+1).

IsobutylGABA oxadiazolone (J) is also named 3-(2-Aminomethyl-4-methyl-pentyl)-4H-[1,2,4]oxadiazole-5-one; HCl

BOC-IsobutylGABA oxadiazolone(0.25 g, 0.835 mmol) was taken up in 4 M HCl in dioxane and allowed to stand 2.5 hours Evaporation followed by recrystallization of the residue from MeCN-Et_2O yielded a tan solid, 53 mg (27%), mp 181-184°C. ^1H NMR (DMSO-d_6) δ 0.80 (d, 6H, J = 6.35 Hz), 1.1 (m, 2H), 1.25 (s, 9H), 1.60 (m, 1H), 2.10 (m, 1H), 2.5-2.8 (m, 4H), 7.95 (s, 3H), 12.39 (s, 1H). MS (APCI) 216 (M+1). Anal. Calcd for $C_9H_{17}N_3O_2 \cdot HCl$: C, 45.86; H, 7.70; N, 17.83; Cl, 15.04. Found: C, 45.40; H, 7.55; N, 16.79; Cl, 15.81.

EXAMPLE 4

Preparation of (2-Aminomethyl-4-methyl-pentyl)-phosphonic acid (9)



1. Preparation of 2-Isobutyl-succinic acid-4-t-butyl eser-1-methyl ester (**2**): 4-methylpentanoic acid methyl ester (10.0 g, 76.8 mmol) is added to a solution of LDA in 150 mL of THF at -78°C under Ar. After 15 minutes, the anion solution is added by cannula to a solution of t-butyl bromoacetate (22.5 g, 115.2 mmol) in 50 mL of THF at -78°C, and the solution is stirred for 45 minutes. The reaction mixture is then warmed to room temperature, and treated with 100 mL of saturated KH_2PO_4. The THF is evaporated, and the organics are extracted into Et_2O (3 × 50 mL). The Et_2O is washed with 10% $Na_2S_2O_3$ and dried with $MgSO_4$. The solvent is evaporated, and the remaining oil is distilled under vacuum (0.1 mm Hg) to give 11.1 g (59% yield) of 2-isobutyl-succinic acid-4-t-butyl ester-1-methyl ester boiling at 65°C to 72°C. NMR (H^1, 400 MHz, $CDCl_3$) δ 0.9 (6H, m); δ 1.2 (1H, m); δ 1.4 (9H, s); δ 1.5 (2H, m); δ 2.3 (1H, dd); δ 2.5 (1H, dd); δ 2.8 (1H, m); δ 3.6 (3H, s).

2. Preparation of 2-Isobutyl-succinic acid-4-t-butyl ester (**3**): 2-isobutyl-succinic acid-4-t-butyl ester-1-methyl ester (11.1 g, 45.4 mmol) and $LiOH \cdot H_2O$ (2.0 g, 47.7 mmol) are stirred in 180 mL of 3:1 IPA/H_2O at room temperature overnight. The reaction mixture is extracted with Et_2O (3 × 25 mL). The aqueous phase is acidified to pH = 4, with saturated KH_2PO_4 and extracted with Et_2O (3 × 50 mL). The Et_2O is dried over $MgSO_4$, and evaporated to give 8.0 g (77% yield) of 2-isobutyl-succinic acid-4-t-butyl ester as an oil. NMR (H^1, 400 MHz, $CDCl_3$) δ 0.9 (6H, m); δ 1.3 (1H, m); δ 1.4 (9H, s); δ 1.6 (2H, m); δ 2.3 (1H, dd); δ 2.6 (1H, dd); δ 2.8 (1H, m).

3. Preparation of 4-Isobutyl-dihydro-furan-2-one (**4**): A solution of 2-isobutyl-succinic acid-4-t-butyl ester (8.0 g, 34.7 mmol) in 100 mL of THF is cooled to 0°C under Ar and borane dimethyl sulphide complex (2.6 g, 34.7 mmol) is added. The reaction mixture is stirred at 0°C for 10 minutes, and at room temperature overnight. The solution is cooled to 0°C and 100 mL of MeOH is added. The solvents are evaporated, and the remaining oil is dried under hi-vacuum for 2 hrs. The oil remaining is taken up in 100 mL of THF, and a catalytic amount of p-toluene sulfonic acid is added. The solution is warmed to reflux overnight. After being cooled to room temperature, the solvent is evaporated, and

the oil is taken up in Et_2O (100 mL). The Et_2O solution is extracted with 2.0N Na_2CO_3 (2 × 50 mL) followed by 100 mL of brine and dried over $MgSO_4$. Evaporation of Et_2O followed by medium pressure chromatography (MPLC) of the remaining oil in 20% EtOAc/Hexanes gives 4.4 g (89% yield) of 4-isopropyl-dihydro-furan-2-one as an oil. NMR (H^1, 400 MHz, $CDCl_3$) δ 0.9 (6H, m); δ 1.3 (2H, dd); δ 1.5 (1H, m); δ 2.1 (1H, m); δ 2.6 (2H, m); δ 3.6 (1H, m); δ 4.4 (1H, m).

4. Preparation of 3-Bromomethyl-3-isobutyl-propionic acid ethyl ester (**5**): A solution of 4-isopropyl-dihydro-furan-2-one (4.4 g, 30.9 mmol) in absolute EtOH (50 mL) is cooled to 0°C and saturated with HBr by passing HBr gas through it for 10 minutes. The solution is warmed to room temperature and stirred for 2.5 hours. It is diluted with 150 mL of brine and extracted with Et_2O (3 × 100 mL). Drying over $MgSO_4$ followed by evaporation of the solvent gives 4.9 g (63% yield) of 3-bromomethyl-3-isobutyl-propionic acid ethyl ester as an oil. NMR (H^1, 300 MHz, $CDCl_3$) δ 0.9 (6H, d); δ 1.3 (5H, m); δ 1.6 (1H, m); δ 2.3 (1H, m); δ 2.5 (1H, dd); δ 3.2 (1H, dd); δ 3.6 (1H, dd); δ 4.1 (2H, q).

5. Preparation of 3-(Diethoxy-phosphorylmethyl)-5-methyl-hexanoic acid ethyl ester (**6**): 3-bromomethyl-3-isobutyl-propionic acid ethyl ester (4.6 g, 18.3 mmol) is warmed in a 170°C oil bath under Ar. Triethyl phosphite (3.6 g, 22 mmol) is added dropwise over 2 hours. When addition is complete, the oil bath temperature is raised to 190°C for 4 hours. The reaction mixture is cooled to room temperature, and the product is purified by MPLC in EtOAc to give 2.7 g (48% yield) of 3-(Diethoxy-phosphorylmethyl)-5-methyl-hexanoic acid ethyl ester. NMR (H^1, 400 MHz, $CDCl_3$) δ 0.8 (6H, d); δ 1.2 (5H, m); δ 1.3 (6H, m); δ 1.6 (1H, m); δ 1.7 (1H, d); δ 1.8 (1H, d); 2.3 (2H, m); δ 2.5 (1H, dd); δ 4.1 (6H, m).

6. Preparation of 3-(Diethoxy-phosphorylmethyl)-5-methyl-hexanoic acid (**7**): 3-(Diethoxy-phosphorylmethyl)-5-methyl-hexanoic acid ethyl ester (1.0 g, 3.2 mmol) and NaOH (1.8 mL, 2.0 M) are combined in 10 mL of EtOH at 0°C. After 15 minutes, the reaction mixture is warmed to room temperature and stirred overnight. The EtOH is evaporated, and 50 mL of 2.0 M NaOH is added. The

solution is extracted with Et_2O (2 × 50 mL), and then acidified to pH = 1 with concentrated HCl. The acidic solution is extracted with EtOAc (3 × 50 mL), and the combined extracts are dried over $MgSO_4$ and evaporated to give 0.65 g (72% yield) of 3-(Diethoxy-phosphorylmethyl)-5-methyl-hexanoic acid as an oil. NMR (H^1, 400 MHz, $CDCl_3$) δ 0.9 (6H, d); δ 1.3 (8H, m); δ 1.6 (1H, m); δ 1.8 (2H, m); δ 2.3 (1H, m); δ 2.5 (2H, m); δ 4.1 (4H, m).

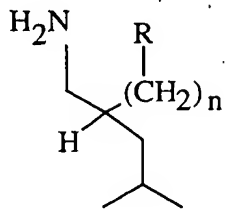
7. Preparation of [2-(Benzyloxycarbonylamino-methyl)-4-methyl-pentyl]-phosphonic acid diethyl ester (**8**): A solution 3-(Diethoxy-phosphorylmethyl)-5-methyl-hexanoic acid (0.65 g, 2.3 mmol), diphenyl-di-phosphoryl-azide (0.76 g, 2.8 mmol), triethyl amine (0.47 g, 4.6 mmol), and benzyl alcohol (0.5 g, 4.6 mmol) in 100 mL of toluene is warmed to reflux overnight. The toluene is evaporated, and the remaining oil is taken up in 50 mL of EtOAc. The EtOAc solution is washed with 1.0N HCl (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and 50 mL of brine. Drying over Na_2SO_4 followed by evaporation of the solvent gives an oil which is purified by MPLC in EtOAc. Yield of [2-(Benzyloxycarbonylamino-methyl)-4-methyl-pentyl]-phosphonic acid diethyl ester = 0.46 g (52%). NMR (H^1, 400 MHz, $CDCl_3$) δ 0.9 (6H, m); δ 1.1-1.4 (9H, m); 1.7 (2H, m); δ 2.0 (1H, m); δ 3.1 (1H, m); δ 3.3 (1H, m); δ 4.1 (4H, q); δ 5.0 (2H, s); δ 5.7 (1H, bs); δ 7.3 (5H, m).

8. Preparation of (2-Aminomethyl-4-methyl-pentyl)-phosphonic acid (**9**): A solution of [2-(Benzyloxycarbonylamino-methyl)-4-methyl-pentyl]-phosphonic acid diethyl ester (0.46 g, 1.2 mmol) in 20 mL of 47% aqueous HBr is warmed at reflux overnight. The solution is cooled to room temperature, and the H_2O is evaporated. The remaining solid is taken up in 10 mL of H_2O, filtered through Celite® 545, and passed through a Dowex® 50 ion exchange column (Bed Volume = 30 mL). The column is eluted with 200 mL of H_2O, 150 mL of 3% NH_4OH, and 150 mL of 10% NH_4OH. The basic eluates are combined and evaporated to give 0.14 g of a white solid. After drying under vacuum at 60°C with P_2O_2, the yield of (2-Aminomethyl-4-methyl-pentyl)-phosphonic acid = 0.11 g (47%). NMR (H^1, 400 MHz, CD_3OD) δ 0.9 (6H, m); δ 1.2 (2H, t);

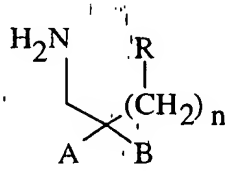
δ 1.4 (1H, m); δ 1.7 (2H, m); δ 2.1 (1H, m); δ 2.7 (1H, dd); δ 3.0 (1H, dd). MS (m/e) 196 (M + 1, 100%). Analysis for $C_7H_{18}NO_3P$: Calculated: C-43.07, H-9.29, N-7.18. Found: C-43.08, H-8.62, N-6.89.

CLAIMS

1. The compounds of the invention are those of formula



and



1A 1B

or a pharmaceutically acceptable salt thereof wherein:

n is an integer of from 0 to 2;

R is sulfonamide,

amide,

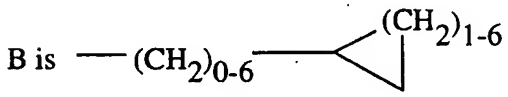
phosphonic acid,

heterocycle,

sulfonic acid, or

hydroxamic acid;

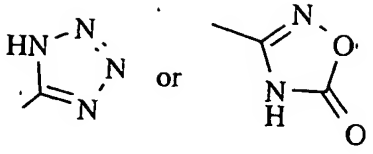
A is hydrogen or methyl; and

B is  ,

straight or branched alkyl of from 1 to 11 carbons, or

$-(CH_2)_{1-4}-Y-(CH_2)_{0-4}$-phenyl wherein Y is -O-, -S-, $-NR'_3$ wherein R'_3 is alkyl of from 1 to 6 carbons, cycloalkyl of from 3 to 8 carbons, benzyl or phenyl wherein benzyl or phenyl can be unsubstituted or substituted with from 1 to 3 substituents each independently selected from alkyl, alkoxy, halogen, hydroxy, carboxy, carboalkoxy, trifluoromethyl, and nitro.

2. A compound according to Claim 1 wherein n is 1, m is 2, and R is



3. A compound according to Claim 1 wherein R is a sulfonamide selected from $-NHSO_2R^{15}$ or $-SO_2NHR^{15}$ wherein R^{15} is straight or branched alkyl or trifluoromethyl.

4. A compound according to Claim 1 named:

4-Methyl-2-(1H-tetrazol-5-ylmethyl)-pentylamine;

3-(2-Aminomethyl-4-methyl-pentyl)-4H-[1,2,4]oxadiazole-5-thione, HCl;

3-(2-Aminomethyl-4-methyl-pentyl)-4H-[1,2,4]oxadiazole-5-one, HCl;

(2-Aminomethyl-4-methyl-pentyl)-phosphonic acid;

3-(3-Amino-2-cyclopentyl-propyl)-4H-[1,2,4]oxadiazol-5-one;

3-(3-Amino-2-cyclopentyl-propyl)-4H-[1,2,4]thiadiazol-5-one;

2-Cyclopentyl-3-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-yl)-propylamine;

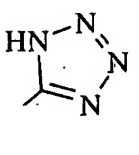
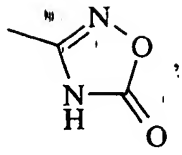
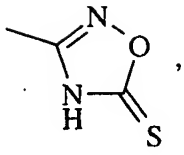
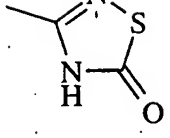
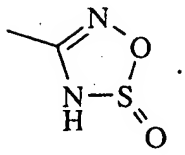
3-(3-Amino-2-cyclobutyl-propyl)-4H-[1,2,4]oxadiazol-5-one;

3-(3-Amino-2-cyclobutyl-propyl)-4H-[1,2,4]thiadiazol-5-one; and

2-Cyclobutyl-3-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-yl)-propylamine.

5. A compound according to Claim 1 wherein R is a phosphonic acid, $-PO_3H_2$.

6. A compound according to Claim 1 wherein R is a heterocycle selected from





, and


7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

8. A method for treating epilepsy comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

9. A method for treating faintness attacks, hypokinesia, and cranial disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

10. A method for treating neurodegenerative disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 o a mammal in need of said treatment.

11. A method for treating depression comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

12. A method for treating anxiety comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

13. A method for treating panic comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

14. A method for treating pain comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

15. A method for treating neuropathological disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

16. A method for treating gastrointestinal damage comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

17. A method for treating inflammation comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

18. A method for treating gastrointestinal disorders, especially irritable bowel syndrome, comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 257/04, A61K 31/41, C07D 271/06, C07F 9/38, A61K 31/66, C07D 291/04 — A3

(11) International Publication Number: WO 99/31074

(43) International Publication Date: 24 June 1999 (24.06.99)

(21) International Application Number: PCT/US98/23917

(22) International Filing Date: 10 November 1998 (10.11.98)

(30) Priority Data:

60/069,773	16 December 1997 (16.12.97)	US
60/104,924	20 October 1998 (20.10.98)	US

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BELLIOTTI, Thomas, Richard [US/US]; 6125 Lodi Lane, Saline, MI 48176 (US). BRYANS, Justin, Stephen [GB/GB]; Dean Cottage, 3 W. Wickham Road, Balsham CB1 6DZ (GB). CAPIRIS, Thomas [US/US]; 14816 Greenbriar Court, Plymouth, MI 48170 (US). HORWELL, David, Christopher [GB/GB]; 8 West Hill, Foxton, Cambridge CB2 6SZ (GB). KNEEN, Clare, Octavia [GB/GB]; Slade Cottage, Petts LN, Little Walden, Essex CB10 1XH (GB). WUSTROW, David, Juergen [US/US]; 5101 John Holmes Road, Ann Arbor, MI 48103 (US).

(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

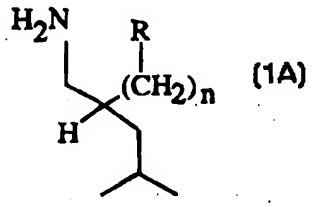
Published

With international search report.

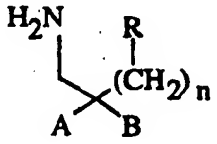
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 4 November 1999 (04.11.99)

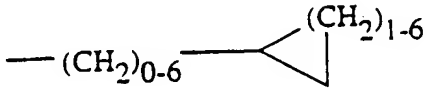
(54) Title: ((CYCLO)ALKYL SUBSTITUTED)-.GAMMA.-AMINOBUTYRIC ACID DERIVATIVES (=GABA ANALOGUES), THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS



(1A)



(1B)



(B)

(57) Abstract

Novel amines of formulas (1A) and (1B) or a pharmaceutically acceptable salt thereof wherein: n is an integer of from 0 to 2; R is sulfonamide, amide, phosphonic acid, heterocycle, sulfonic acid, or hydroxamic acid; A is hydrogen or methyl; and B is (a), straight or branched alkyl of from 1 to 11 carbons, or $-(CH_2)_{1-4}-Y-(CH_2)_{0-4}$-phenyl wherein Y is -O-, -S-, $-NR'_3$ wherein R'_3 is alkyl of from 1 to 6 carbons, cycloalkyl of from 3 to 8 carbons, benzyl or phenyl wherein benzyl or phenyl can be unsubstituted or substituted with from 1 to 3 substituents each independently selected from alkyl, alkoxy, halogen, hydroxy, carboxy, carboalkoxy, trifluoromethyl, and nitro are disclosed and are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, inflammatory diseases, and gastrointestinal disorders, especially IBS. Processes for the preparation and intermediates useful in the preparation are also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23917

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D257/04 A61K31/41 C07D271/06 C07F9/38 A61K31/66
C07D291/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 465 803 A (HEATH R.L. & PIGGOTT H.A.) 29 March 1949 see reduction products of examples 4,5,7-9,11,12 ---	1
X	US 2 866 786 A (FEICHTINGER H. & TUMMES H.) 30 December 1958 see column 3, line 50 - line 52 ---	1
X	RIEMSCHNEIDER R. & KAMPFER H.: "Zur Kenntnis der cis-trans-Asymmetrie. XI. Optische Aktivität von cis,trans-1,3-Bis-[.alpha.-phenylcinnamoyl amino]-2-methyl-2-n-propyl-propan" JUSTUS LIEBIEGS ANNALEN DER CHEMIE, vol. 665, 1963, pages 35-42, XP002098848 see formula VIII see page 37 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 1999	23.09.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hartrampf, G

1

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/US 98/23917

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARKOV V.I. & BURMISTROV S.I.: "1-(Arylsulfonyl)-2,2-dimethylaziridines. II. Reactions with ammonia amines, arenesulfonamides, and phthalimide" THE JOURNAL OF GENERAL CHEMISTRY, USSR, vol. 35, no. 1, January 1965, pages 158-161, XP002098849 see formula I see section experimental, first and second compound see page 159 ---	1
X	BOSNICH B. & DWYER F.P.: "Mixed bidentate and tridentate complexes of cobalt" AUSTRALIAN JOURNAL OF CHEMISTRY, vol. 19, 1966, pages 2045-2050, XP002098850 see page 2050, paragraph 2 ---	1
X	VINOT N.: "No. 683. Synthèse de cyanométhyl-2 benzimidazoles .alpha.-substitués. Leur utilisation à la préparation de benzimidazoles possédant d'autres fonctions" BULLETIN DE LA SOCIÉTÉ CHIMIQUE DE FRANCE, no. 12, 1966, pages 3989-3993, XP002098851 see formula 4 see second compound see page 3992, column 2 ---	1
X	TENTHOREY P.A. ET AL.: "New antiarrhythmic agents. 3. Primary .beta.-amino anilides" JOURNAL OF MEDICINAL CHEMISTRY, vol. 22, no. 10, October 1979, pages 1182-1186, XP002098852 see compounds 35 and 36 see page 1184; table II ---	1
X	FOKIN A.V. ET AL.: "The fluoroacylation of diamines" BULL. ACAD. SCI. USSR, DIV. CHEM. SCI., vol. 30, no. 4, April 1981, pages 643-646, XP002098853 see formulae IIIa and VI see page 644; table 1 ---	1
X	EP 0 061 673 A (ASAHI KASEI KOGYO KABUSHIKI KAISHA) 6 October 1982 see example 15; tables 9-1 ---	1

-/--

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23917

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 103, no. 15, 14 October 1985 Columbus, Ohio, US; abstract no. 122998x, "Aminoalkylsulfonic acids" page 683; column 2; XP002098857 see abstract & JP 60 023360 A (MITSUI TOATSU CHEMICALS, INC.) 5 February 1985 ---	1
X	HANKOVSZKY O.H. ET AL.: "New antiarrhythmic agents. 2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides and 2,2,5,5-tetramethylpyrrolidine-3-carboxamides" JOURNAL OF MEDICINAL CHEMISTRY, vol. 29, no. 7, 1986, pages 1138-1152, XP002068557 see compound 1e see page 1141 ---	1
X	SERGEEV G.B. & KOMAROV V.S.: "Organic reactions in the solid phase prepared by co-deposition of reagent vapours onto cold surface" MOLECULAR CRYSTALS AND LIQUID CRYSTALS (INC. NONLINEAR OPTICS), vol. 156, 1988, pages 129-138, XP002098854 see compound II see page 136 ---	1
X	EP 0 506 532 A (LIPHA, LYONNAISE INDUSTRIELLE PHARMACEUTIQUE) 30 September 1992 see intermediate of compound 9 see claim 7, formula 5 ---	1
X	O'BRIEN P.M. ET AL.: "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 8. Incorporation of amide or amine functionalities into a series of disubstituted ureas and carbamates. Effects on ACAT inhibition in vitro and efficacy in vivo" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 12, 1994, pages 1810-1822, XP002082610 see scheme 5, compound 23d ---	1
X	EP 0 678 503 A (CIBA-GEIGY AG) 25 October 1995 see page 75, line 37; example 123 ---	1
	-/--	

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23917

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 05201 A (BRITISH BIOTECH PHARMACEUTICALS) 22 February 1996 see claim 22(viii), formula XXI see example 11(b) ---	1
X	BELLEMIN R. ET AL.: "New indole' derivatives as ACAT inhibitors: Synthesis and structure-activity relationships" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, CHIM. THER., vol. 31, no. 2, 1996, pages 123-132, XP004040099 see scheme 1, compound 2m see page 126; table II ---	1
X	LUCET D. ET AL.: "Highly stereoselective conjugate addition of (R)- or (S)-4-phenyl-2-oxazolidinone to nitroalkenes" JOURNAL OF ORGANIC CHEMISTRY, vol. 62, no. 9, April 1997, pages 2682-2683, XP002098855 see scheme 1, first formula see page 2683 ---	1
X	WHITLOCK G.A. & CARREIRA E.M.: "Enantioselective synthesis of ent-Stellettamide A via a novel dipolar cycloaddition reaction of (trimethylsilyl)diazomethane" JOURNAL OF ORGANIC CHEMISTRY, vol. 62, no. 23, November 1997, pages 7916-7917, XP002098856 see scheme 2, precursor of 17 see page 7917 ---	1
Y	KRAUS J.L.: "Isosterism and molecular modification in drug design: Tetrazole analogue of GABA: Effects on enzymes of the .gamma.-aminobutyrate system" PHARMACOLOGICAL RESEARCH COMMUNICATIONS, vol. 15, no. 2, 1983, pages 183-189, XP002096228 see the whole document ---	1,3-7
Y	BURGER A.: "Isosterism and bioisosterism in drug design" PROGRESS IN DRUG DESIGN, vol. 37, 1991, pages 287-371, XP002096229 see page 332 - page 338 ---	1,3-7
Y	WO 92 09560 A (NORTHWESTERN UNIVERSITY) 11 June 1992 see the whole document --- -/--	1,3-7

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23917

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KERR D.I.B. & ONG J.: "GABA agonists and antagonists" MEDICINAL RESEARCH REVIEWS, vol. 12, no. 6, 6 November 1992, pages 593-636, XP002080823 see page 620 - page 628 ---	1,3-7
Y	HOWSON W. ET AL.: "Biological activity of 3-aminopropyl (methyl) phosphinic acid, a potent and selective GABA(B) agonist with CNS activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 3, no. 4, 1993, pages 515-518, XP002096230 see the whole document ---	1,3-7
Y	PATANI G.A. & LA VOIE E.J.: "Bioisosterism: A rational approach in drug design" CHEMICAL REVIEWS, vol. 96, no. 8, 1996, pages 3147-3176, XP000652176 see 3. Carboxylate group bioisosteres see page 3168, left-hand column - page 3170, left-hand column ---	1,3-7
P,Y	WO 98 17627 A (WARNER-LAMBERT COMPANY) 30 April 1998 see the whole document -----	1,3-7

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/23917

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8-18
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [X] Claims Nos.: 2
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

Dependent claim 2 defines an integer m, which appears neither in formula 1A nor in formula 1B.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/23917

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2465803 A	29-03-1949	NONE	
US 2866786 A	30-12-1958	CH 325458 A	
		DE 932676 C	
		FR 1100176 A	16-09-1955
		GB 752227 A	
EP 61673 A	06-10-1982	JP 1044188 B	26-09-1989
		JP 1557669 C	16-05-1990
		JP 58121278 A	19-07-1983
		JP 1601704 C	27-02-1991
		JP 2027992 B	20-06-1990
		JP 58121279 A	19-07-1983
		JP 1499131 C	29-05-1989
		JP 57156463 A	27-09-1982
		JP 63048869 B	30-09-1988
		JP 1508507 C	26-07-1989
		JP 57200366 A	08-12-1982
		JP 63061942 B	30-11-1988
		US 4456757 A	26-06-1984
		US 4525589 A	25-06-1985
		US 4560755 A	24-12-1985
EP 506532 A	30-09-1992	FR 2674522 A	02-10-1992
		AT 111078 T	15-09-1994
		AU 658609 B	27-04-1995
		AU 1309492 A	01-10-1992
		CA 2063170 A	27-09-1992
		CS 9200895 A	14-10-1992
		DE 69200378 D	13-10-1994
		DE 69200378 T	09-03-1995
		DK 506532 T	20-02-1995
		ES 2064149 T	16-01-1995
		HU 65489 A	28-06-1994
		IE 65366 B	18-10-1995
		IL 101248 A	05-12-1996
		JP 5097802 A	20-04-1993
		KR 9507753 B	14-07-1995
		MX 9201365 A	01-10-1992
		NO 178260 B	13-11-1995
		NZ 242078 A	26-10-1994
		OA 9573 A	31-01-1993
		SI 9210305 A	29-02-1996
		RU 2074179 C	27-02-1997
		US 5219859 A	15-06-1993
		ZA 9202163 A	27-09-1993
EP 678503 A	25-10-1995	AU 1642095 A	26-10-1995
		AU 699616 B	10-12-1998
		AU 1642195 A	26-10-1995
		AU 1642395 A	26-10-1995
		CA 2147044 A	19-10-1995
		CA 2147052 A	19-10-1995
		CA 2147056 A	19-10-1995
		CN 1117960 A	06-03-1996
		CZ 9500976 A	15-11-1995
		EP 0678514 A	25-10-1995
		EP 0678500 A	25-10-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/23917

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 678503 A		FI 951771 A	19-10-1995
		FI 951772 A	19-10-1995
		FI 951773 A	19-10-1995
		HU 74074 A	28-10-1996
		HU 72110 A	28-03-1996
		HU 71701 A	29-01-1996
		JP 8053434 A	27-02-1996
		JP 8081430 A	26-03-1996
		JP 8027079 A	30-01-1996
		NO 951441 A	19-10-1995
		NO 951442 A	19-10-1995
		NO 951443 A	19-10-1995
		NZ 270936 A	24-06-1997
		NZ 270938 A	26-11-1996
		NZ 270939 A	20-12-1996
		US 5606078 A	25-02-1997
		US 5659065 A	19-08-1997
		US 5559111 A	24-09-1996
		US 5654445 A	05-08-1997
		US 5646143 A	08-07-1997
		US 5627182 A	06-05-1997
		US 5705658 A	06-01-1998
		ZA 9503050 A	08-11-1995
		ZA 9503051 A	18-10-1995
		ZA 9503052 A	18-10-1995
WO 9605201 A	22-02-1996	AU 3186395 A	07-03-1996
		EP 0775139 A	28-05-1997
		US 5753671 A	19-05-1998
WO 9209560 A	11-06-1992	AU 9137091 A	25-06-1992
		MX 9102241 A	31-01-1994
		US 5563175 A	08-10-1996
		US 5684189 A	04-11-1997
		US 5608090 A	04-03-1997
		US 5599973 A	04-02-1997
		US 5710304 A	20-01-1998
		US 5847151 A	08-12-1998
WO 9817627 A	30-04-1998	AU 4669797 A	15-05-1998
		HR 970560 A	31-08-1998